

Diagnosis, Treatment, and Follow-Up of Borderline Ovarian Tumors

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Compare the epidemiologic and reproductive risk factors in BOTs with those in ovarian cancers and describe the molecular background of development of BOTs.
2. Use the pathological terminology with either original grouping of borderline category or new subclassification of BOTs and assess the major predictor of recurrence and survival.
3. Determine an appropriate diagnostic algorithm for patients with symptoms suggesting malignant ovarian tumors that will identify borderline ovarian tumors when present.

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ABSTRACT

Borderline ovarian tumors represent a heterogeneous group of noninvasive tumors of uncertain malignant potential with characteristic histology. They occur in younger women, are present at an early stage, and have a favorable prognosis, but symptomatic recurrence and death may be found as long as 20 years after therapy in some patients. The molecular changes in borderline ovarian tumors indicate linkage of this disease to type I ovarian tumors (low-grade ovarian carcinomas). The pathological stage of disease and subclassification of extraovarian disease into invasive and noninvasive implants, together with the presence of postoperative macroscopic residual disease, appear to be the major predictor of recurrence and survival. However, it should be emphasized that the most important negative prognostic factor for recurrence is just the use of conservative surgery, but without any impact on patient

survival because most recurrent diseases are of the borderline type—easily curable and with an excellent prognosis. Borderline tumors are difficult masses to correctly preoperatively diagnose using imaging methods because their macroscopic features may overlap with invasive and benign ovarian tumors. Over the past several decades, surgical therapy has shifted from a radical approach to more conservative treatment; however, oncologic safety must always be balanced. Follow-up is essential using routine ultrasound imaging, with special attention paid to the remaining ovary in conservatively treated patients. Current literature on this topic leads to a number of controversies that will be discussed thoroughly in this article, with the aim to provide recommendations for the clinical management of these patients. *The Oncologist* 2012;17:1515–1533

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INTRODUCTION

Borderline ovarian tumors (BOTs) form a separate entity within the group of epithelial ovarian tumors acknowledged by the International Federation of Gynecology and Obstetrics (FIGO) in 1961 and adopted by the World Health Organization (WHO) in 1973. Three terms are currently used to refer to these tumors: borderline tumor, tumor of low malignant potential, and atypical proliferative tumor [1]. Not only is there confusion regarding the optimal terminology, diagnostic difficulties concerning preoperative imaging methods, tumor markers, frozen section, final pathological assessment, and uncertainty in the definition of reliable prognostic parameters often accompanies these tumors. The radicality of surgical procedures, especially in younger patients for whom preserving fertility is a consideration, completion of surgical staging, and the type of operative approach (laparoscopy vs. laparotomy) often remain the topics of debate. Lastly, postoperative treatment (e.g., adjuvant chemotherapy, infertility and in vitro fertilization drugs, hormonal replacement therapy, completion of surgery after finishing reproductive plans) and follow-up strategies are often discussed. Borderline tumors remain a controversial issue. This review will attempt to inform readers about the recent data concerning these topics.

EPIDEMIOLOGY

Borderline ovarian tumors comprise about 15%–20% of all epithelial ovarian malignancies [2, 3] with an incidence of 1.8–4.8 per 100,000 women per year [3–5]. BOTs differ significantly from ovarian carcinomas with regard to percentile distribution of tumor histotypes, lower FIGO stage, excellent overall prognosis, younger age distribution, higher infertility rate, and a lower frequency of BRCA mutations.

The increased incidence of BOTs within ovarian malignant tumors has been observed in recent decades worldwide together with slightly decreasing incidence of ovarian cancer [6]. In Sweden, the incidence of BOTs increased from 1.0 to 5.3 per 100,000 women per year between 1960 and 2005, while the distribution of BOTs among ovarian malignant tumors increased from 5%–10% to 25% [3]. This trend may reflect more accurate pathological diagnosis of BOTs and/or the potential change of risk factors contributing to the development of BOTs. In particular, there are studies showing no protective effect of hormonal contraceptives against BOTs as opposed to ovarian cancers [3, 7]; however, the results of further studies concerning BOTs and hormonal contraceptives are controversial, as discussed later. The increased risk of BOTs may also be associated with the use of fertility drugs [8].

The majority of BOTs are serous tumors (53.3%), followed by mucinous tumors (42.5%) and less common histotypes (4.2%). In ovarian cancers, the serous histotype is also most common, whereas the mucinous histotype is very rare (<10%) [9]. BOTs are mainly diagnosed at an earlier stage (75% at FIGO stage I) in contrast to ovarian cancer (25% at FIGO stage I) [10]. In a review of 15 studies, which included a total of 948 patients, 69.6% (660) of borderline tumors included in the studies occurred in stage I, 10.3% (98) in stage II, 19.2% (182) in stage III, and 0.6% (6) in stage IV [11]. Similar results were

found in a systematic review of 6,362 patients by du Bois et al.: 78.9% of patients with BOTs were diagnosed at FIGO stage I and 21.1% at FIGO stages II–IV, although FIGO stage IV represents an exception [9].

Even though the prognosis for most patients with BOTs is excellent, a minority will have a more aggressive form and eventually die from their disease. The 5-year survival rate for women with stage I borderline tumors is approximately 95%–97%, but the 10-year survival rate is only 70%–95%, caused by late recurrence. The 5-year survival rate for stage II–III patients is 65%–87% [12]. If survival is specified to major histological types, Sherman et al. reported in a population-based analysis that the overall relative survival rate at 10 years was $96.9\% \pm 2.3\%$ for serous BOTs and $94.0\% \pm 3.1\%$ for mucinous BOTs. The survival rate at 10 years for advanced serous BOTs was $89.9\% \pm 5.3\%$. The survival data for 10 years for advanced mucinous BOTs are limited: at 5 years, it reached $85.5\% \pm 9.0\%$. It should be noted that the data concerning primary ovarian mucinous tumors must be taken with caution, as this group of patients was associated with an excess of second tumors of the digestive tract that possibly caused the misdiagnosis of primary ovarian tumor [10]. Finally, it should also be noted that the 5-year survival rate of BOTs and ovarian cancer increased from 1960 to 2000 (70%–80% vs. 90% for BOTs; 30% vs. 50% for ovarian cancers) [13].

Patients with borderline ovarian tumors are, in general, 10 years younger than women with epithelial ovarian cancer (45 vs. 55 years) [14, 15]. A third of patients diagnosed with BOTs are younger than 40 years of age and frequently are candidates for fertility-sparing surgery [3, 10]. Borderline tumors are rarely seen in women with BRCA mutations [16]. Although a few cases of BOTs have been reported in BRCA mutation carriers, it rather reflects the prevalence of these mutations in the general population. In a nationwide study in Israel, the prevalence of Jewish founder mutations in BRCA1 and BRCA2 was significantly lower, occurring in only 4.3% of patients with early BOTs compared with 24.2% of patients with early-stage ovarian cancer (24.2%) [17].

Other epidemiologic characteristics do not differ significantly between BOT and ovarian carcinomas, and epidemiological studies have also confirmed similar reproductive risk factors in BOTs as in ovarian cancers, except for higher frequency of infertility [18, 19]. Rather than a single hypothesis, an overlap in mechanisms involved in each hypothesis may more likely explain the reproductive risk factors in full. The incessant ovulation hypothesis assumes that the development of ovarian malignant tumor is a consequence of repeated microtrauma to the ovarian surface epithelium (OSE) during ovulation [20]. The inhibition of ovulation could explain the protective influence of pregnancy, breastfeeding, and hormonal contraception.

In a Swedish case-control study, increasing parity and lactation reduced the risk of borderline ovarian tumors in women aged 50–74 years; in contrast to previous studies, no protection followed oral contraceptive use [21]. Other studies presented a protective trend of oral contraceptives for BOTs; the absence of significance is probably related to the smaller num-

ber of cases [18–19, 22–23]. A comparable level of protection by oral contraceptives for serous BOT was also confirmed in a Danish case-control study [23]. The protective effect for oral contraceptives could be also explained by inhibition of gonadotropin levels. The gonadotropin hypothesis states that the malignant transformation can be caused by the exposure of OSE to excessive gonadotropin levels. Some case-control studies noted a two- to fourfold increased risk of BOTs after the use of fertility drugs followed by ovarian stimulation and multiple ovarian punctures [8]. Following this trend, a high proportion of serous borderline ovarian tumors were observed after ovarian stimulation for in vitro fertilization [8, 24]. The hormonal hypothesis presumes a decisive role for ovarian hormones, progesterone in particular. The experimental data allow speculation that progesterone may lead to a “clearing” of cells in OSE containing sublethal DNA damage by the induction of apoptosis. Hormonal situations, such as unopposed estrogen use and obesity, where estrogens are not counteracted by progestins may also increase the risk of serous tumors [21]. Moreover, androgens may promote tumor cell promotion. A higher androgen level is associated with polycystic ovary syndrome (PCOS). An Australian population-based case-control study showed that serous borderline tumors were positively associated with a history of PCOS (odds ratio [OR]: 2.6; 95% confidence interval [CI]: 1.0–6.1) [25].

The mechanisms that can reduce the development of endometriosis may be a factor in risk reduction, as endometriosis is a precursor of some BOTs (e.g., endometrioid or clear-cell BOTs). The mechanisms for risk reduction include hysterectomy or tubal ligation; hence, both may prevent passage of endometrial tissue via retrograde menstruation, which is one of the proposed mechanisms for the development of this disease. Furthermore, hysterectomy and tubal ligation prevent the introduction of a variety of potential environmental carcinogens from entering the peritoneal cavity and thereby coming into contact with tubal and ovarian tissue [15, 26]. Both endometriosis and external carcinogens (e.g., talc, asbestos) may also participate in the inflammation hypothesis associated with carcinogenesis [26].

MOLECULAR BACKGROUND

Epithelial ovarian tumors, including borderline tumors, represent a rather heterogeneous group with common origins in tubal or ovarian surface epithelium or epithelial inclusion cysts. Tumors of the same morphology can be found in all structures developmentally derived from Müllerian ducts. Many authors presume that these tumors originate from common stem or progenitor cells as a result of genetic and epigenetic changes. As in other malignancies (breast cancer, colorectal cancer), there is increasing evidence supporting tumor stem cell theory. Recent projects dealing with promoter methylation analyses found typical methylation patterns confirming clonal origin of tumors from stem cells [27, 28].

In each tissue type, we can identify (or at least presume) three basic cell populations necessary for development and recovery of this tissue:

1. Tissue-specific stem cells: The replicative potential of these cells is comparable to the lifetime of the organism. They serve as a basic source for recovery of tissue of all the types of specialized cells and represent a minority population of the cells.
2. Progenitor cells: These cells are the closest daughter cells of stem cells. They have limited but rapid replicative potential, and they can migrate and differentiate to specialized cells.
3. Specialized cells: These cells constitute more than 99% of cell population in tissue. They have distinctively limited replicative potential and their lifetime is only a small part of the organism's lifetime. They execute all specific tissue functions.

The key features of tumor cells are unlimited replication, dedifferentiation, and loss of contact inhibition. Hence, it is likely that a primary clone of transformed cells (tumor stem cells) originates due to gradual accumulation of genetic and epigenetic changes from stem or progenitor cells rather than from specialized cells. During such an accumulation, the tumor population of first benign, then borderline and finally malignant characteristics could be stepwise generated. Specialized tissue cells represent subsequently generated advanced genomic changes in stem or progenitor cells (tumor stem cells), and this tumor population mirrors genomic changes in their stem cells.

Thanks to recent molecular genetic studies, two major types of epithelial ovarian tumors can be distinguished. These types differ in molecular changes during carcinogenesis and in biological behavior. This classification describes different molecular pathways of carcinogenesis rather than relationship to any histotype. Type I tumors (so-called low-grade tumors) typically develop slowly and gradually from benign through borderline to malignant lesions. Type II tumors (so-called high-grade tumors) rapidly become progredient without known preinvasive lesions [29, 30]. No precise prognostic or predictive markers exist to clearly distinguish between tumors of purely benign behavior and those with malignization potential, making clinical management of BOTs difficult. With definition of molecular factors predicting biological nature and malignant potential of borderline tumors, clinicians may be able to better predict which patients should be offered fertility-sparing procedures with no risk or acceptably low risk of recurrence and which patients should not be candidates for conservative surgery due to aggressive potential of the tumor.

Genomic changes of the tumor, rather than pure tumor morphology, seem to be a better tool for BOT biological behavior recognition. Projects addressing this field of research, however, are relatively rare. The majority of them deal with the most common type of BOT (i.e., serous BOT) and serous low-grade cancer. There is a consensus that early events in the carcinogenesis of low-grade serous tumors are represented by mutations in *KRAS* and/or *BRAF* genes (Table 1). Protein products of both of these genes act as start regulators of transduction cellular pathways RAS/RAF/MEK/MAPK. Oncogenic mutations in codons 12 or 13 in *KRAS* and in codon 599 in *BRAF* lead to constitutive activation of this pathway and thus induce processes leading to tumor transformation of the cell.

Table 1. Carcinogenesis of borderline ovarian tumors and genomic alterations

BOT	Precursor	Progression to invasive tumor	Cytogenetics
Serous	Cystadenoma	Progression to low-grade serous carcinoma	Mutations in <i>KRAS</i> or <i>BRAF</i> genes
Mucinous	Cystadenoma (precursor of intestinal subtype of mucinous BOT)	Progression to intraepithelial carcinoma then to mucinous carcinoma	Mutations in <i>KRAS</i> (codons 12 and 13)
	Endometriosis, typically endometriotic cysts (endometriomas); precursor of Müllerian subtype of mucinous BOT	Progression to intraepithelial carcinoma then to mucinous carcinoma	
Endometrioid	Endometriosis, typically endometriotic cysts (endometriomas) or endometrioid adenofibroma	Progression to intraepithelial carcinoma then to low-grade endometrioid carcinoma	Mutations in β -catenin gene; <i>PTEN</i> mutation or LOH; microsatellite instability
Clear cell	Endometriosis, typically endometriotic cysts (endometriomas) or clear-cell adenofibroma	Progression to intraepithelial carcinoma then to clear-cell carcinoma	Mutations in β -catenin gene; <i>PTEN</i> mutations or LOH; microsatellite instability
Brenner (transitional cell)	Benign Brenner	Progression to malignant Brenner tumor	Not yet identified

Abbreviations: BOT, borderline ovarian tumor; LOH, loss of heterozygosity.

The prevalence of *KRAS* and *BRAF* mutations is higher in benign cystadenomas with minor portions of BOT than in pure benign cystadenomas. This can be explained in two ways: (a) analysis of these mutations could better predict the presence of BOT part in the tumor or (b) some benign tumors have the potential to progress into BOT and malignant tumors. *KRAS* and *BRAF* mutations were not found in type II tumors; nevertheless, the constitutive activation of RAS/RAF/MEK/MAPK pathways in these tumors was reported, implicating another way of genomic alteration, probably the affected methylation of promoter regions [31]. Allelic imbalance, loss of heterozygosity (LOH), amplification, or aneuploidy is often found in BOT and type I cancers, although in different loci. In type I tumors, regions on chromosome 1 are affected; in type II tumors, regions of chromosomes 13 and 17 are mainly affected.

In nonserous type I tumors, the molecular characteristics differ slightly from serous tumors (Table 1). For mucinous tumors, mutations in *KRAS*, but not in *BRAF*, are typical. Mutations of β -catenin are often found in the endometrioid, as well as in clear cell tumors together with LOH or mutation of *PTEN* (chromosome 10).

A limited number of studies focused on molecular changes in peritoneal implants of BOT. Studies based on X chromosome inactivation patterns described distinct origins of ovarian tumor and implants, whereas others found the same molecular changes in ovarian tumor and implants. Analyses published so far have identified genomic areas and mechanisms involved in BOT carcinogenesis. However, results are still fragmentary and not suitable to be led into clinical practice. Other studies are still needed to integrate current approaches and to work with larger sample sets.

PATHOLOGY

Borderline tumors have been identified in all epithelial subtypes, including endometrioid, clear cell, Brenner (transitional cell) and mixed epithelial tumors. Serous (53.3%) and mucinous histologies (42.5%) are most common; the data are derived from a review of 5,807 patients provided by du Bois et al. [9]. Borderline ovarian tumors are generally characterized by increased epithelial proliferation accompanied by nuclear atypias (usually mild to moderate) and mildly increased mitotic activity. Stromal invasion, however, is not displayed in this tumor entity.

Serous BOT

According to the most recent edition of the WHO classification of ovarian tumors, serous BOTs are divided into typical serous borderline tumors (90%) and borderline tumors with micropapillary patterns (5%–10%) [32]. Recent studies show that serous BOTs represent a wide spectrum of tumors with different biological potential [33, 34]. Based on the overall favorable prognosis of nonmicropapillary serous BOTs, these investigators have recommended abandoning the borderline category of serous tumors, restricting them to benign and malignant type [33]. In particular, serous BOTs were subclassified into tumors that behave in a benign fashion, called atypical proliferative serous tumors (APSTs, supplemental online Fig. 1), and into low-grade malignant tumors, which include noninvasive micropapillary serous carcinomas (MPSCs; i.e., borderline tumors with a micropapillary pattern according to WHO classification; supplemental online Fig. 2) and APSTs with invasive peritoneal implants (Table 2) [26]. Please note that the invasive form of MPSCs (invasive MPSCs) is synonymous with low-grade serous carcinoma, which can cause some confusion among clinicians. To date, there is no consensus among

Table 2. Histological classification of borderline ovarian tumors

Type	Subtype ^a		Other histological characteristics
	WHO	Blaustein	
Serous	Typical subtype (90%)	Benign group, APSTs	Microinvasion ^c : (a) Usual type (eosinophilic type), which are cells with ample eosinophilic cytoplasm (in 10% serous borderline tumors); (b) less common type (also called microinvasive carcinoma). The structures are identical in appearance to invasive low-grade micropapillary serous carcinoma. ^d Implants can be noninvasive (desmoplastic type or epithelial type) or invasive.
	Micropapillary subtype (10%) ^b	Low grade malignant group: Noninvasive micropapillary serous carcinoma (MPSC) ^b Low grade malignant group: APST with invasive peritoneal implants	
Mucinous	Intestinal subtype (85%)		Mucinous borderline tumor with microinvasion and/or intraepithelial carcinoma ^e
	Müllerian subtype (15%)		Microinvasion and/or intraepithelial carcinoma, ^e as well as peritoneal implants, may be present.
Endometrioid	Adenofibromatous appearance Glandular/papillary appearance		Endometrioid borderline tumor with microinvasion and/or intraepithelial carcinoma ^e and/or extraovarian implants
Clear cell			Clear-cell borderline tumor with microinvasion ^c and/or intraepithelial carcinoma ^e
Brenner (transitional cell)			Resembling low-grade papillary urothelial carcinoma of the urinary tract

^aSubtypes are from the World Health Organization [32] and *Blaustein's Pathology of the Female Genital Tract* [26].
^bEither a ≥ 5 -mm confluent area or 10% of the tumor displaying micropapillary growth is required for diagnosis of micropapillary serous borderline tumors [26].
^cLesion(s) must be < 5 mm [26] or one or more foci should not exceed 10 mm² [32].
^dLimited evidence suggests that this type of microinvasion represents true invasive potential of the tumor.
^eBOT with high-grade atypia without invasion.
Abbreviations: APST, atypical proliferative serous tumor; BOT, borderline ovarian tumor; WHO, World Health Organization.

pathologists whether to retain the original grouping of borderline category or to designate serous BOTs with a micropapillary pattern and/or with invasive implants as carcinomas. Two distinct types of lesions have been designated as microinvasions in borderline tumors (supplemental online Fig. 3, Table 2). To disclose more extensive invasion, a sampling of at least two sections per centimeter of maximum tumor dimension is needed in such cases [35].

Serous borderline tumors are often associated with serous lesions involving the peritoneum (so-called implants). In typical serous BOTs, approximately 35% of patients have implants; this number is even higher if a micropapillary pattern or microinvasion has been identified [32]. These implants are either invasive or noninvasive, depending on their microscopic appearance. Among patients with implants, invasive implants are found in one-fourth of patients and noninvasive implants in

three-fourths of patients [9, 11, 15]. The most invasive implants occur in patients with the micropapillary type of serous BOTs. Discovery of invasive implants in a typical serous BOT (APST) is very rare and most likely related to insufficient sampling of primary ovarian tumors with unsampled micropapillary areas or areas of microinvasion [34, 36].

Lymph nodes of patients with serous borderline tumors commonly show endosalpingiosis (45%) and proliferative serous lesions (up to 42%) [26]. These proliferative serous lesions (consisting either of individual cells with abundant eosinophilic cytoplasm and/or their clusters or characterized by glandular and papillary structures) show strong association with invasive peritoneal implants [37] and micropapillary architecture [38]. However, the presence of lymph node involvement by proliferative serous lesions seems not to be an adverse prognostic factor. In addition, the term *lymph node involve-*

ment (not *metastases*) is preferred [36] because the proliferative serous lesions in lymph nodes may or may not be related to the ovarian tumors.

Mucinous BOTs

Mucinous BOTs are classified as gastrointestinal (or intestinal) type (85%, supplemental online Fig. 4) and endocervical-like type (also referred as Müllerian or seromucinous, 15%), depending on the histological architecture and type of tumor cells. Mucinous tumors with high-grade atypias without invasion are classified as BOTs with intraepithelial carcinoma (supplemental online Fig. 5). Mucinous BOTs with early stromal invasion up to 10 mm² are called microinvasive mucinous BOTs (supplemental online Fig. 6). Borderline tumors with intraepithelial carcinoma and/or microinvasion provide evidence that these tumors form a morphologic spectrum with individual types representing steps in the sequence of mucinous carcinogenesis in the ovary [26]. This finding is supported by similar patterns of *KRAS* mutations and LOH in mucinous borderline ovarian tumors and mucinous ovarian cancer [39]. Mucinous tumors of the ovary are heterogeneous, and one tumor can show areas with benign, borderline and malignant features. Thorough sampling is therefore required to achieve a correct diagnosis and rule out invasion. The previous recommendation of one section per centimeter of maximum tumor dimension seems to be insufficient; at least two sections per centimeter are needed, specifically if the tumor is >10 cm [35, 36].

The gastrointestinal type of mucinous BOTs does not present with peritoneal implants; therefore, the advanced stage of this subtype of primary ovarian mucinous borderline tumor does not exist [36]. If the advanced stage is detected, careful examination of the appendix and intestine is warranted to exclude an occult extraovarian primary tumor simulating the primary ovarian mucinous borderline tumor with intraepithelial carcinoma. Alternatively, it is also possible that foci of destructive invasion representing existing primary ovarian carcinomas were unsampled [26].

Endocervical-type mucinous borderline tumors (supplemental online Fig. 7) may reflect the morphologic and behavioral features that are shared with serous tumors; they may present with implants. For that reason, the term *seromucinous* seems to be more accurate than *endocervical-type* of mucinous borderline tumor [40].

The other types of mucinous tumors encountered in the ovary include metastatic mucinous carcinomas, most commonly from the gastrointestinal tract (biliary tract, pancreas, colon) or endocervix, and low-grade mucinous tumors of appendiceal origin secondarily involving the ovary in association with the clinical syndrome of pseudomyxoma peritonei. Some metastatic mucinous carcinomas can manifest histological features suggestive of their primary ovarian origin. These features include cystadenomas or borderline-like growth patterns, which can be dominant or exclusive [41]. These tumors, especially if they present synchronously or earlier as the first manifestation of disease, can easily be misinterpreted as primary mucinous tumors. In contrast to primary mucinous

BOTs, which are typically larger, unilateral, and confined to the ovarian stroma without surface involvement, the metastatic lesions in the ovaries are often smaller, bilateral, involve surface and superficial cortex [36]. For many years, pseudomyxoma peritonei (i.e., the presence of mucinous ascites or mucoid nodules adherent to peritoneal surfaces) was thought to result from ovarian borderline tumors, but it has recently been revealed that virtually all ovarian tumors associated with pseudomyxoma peritonei represent metastases from ruptured primary low-grade (adenomatous) mucinous tumors of the appendix [42]. The rare exception to the gastrointestinal origin of pseudomyxoma peritonei is the occurrence of mucinous tumors arising in ovarian mature cystic teratomas [43, 44].

Uncommon Borderline Ovarian Tumors (Endometrioid, Clear Cell, Transitional Cell, or Mixed Epithelial Tumors)

Uncommon subtypes of borderline ovarian tumors encompass 3%–4% of all these tumors; they include endometrioid, clear cell, transitional (Brenner) borderline tumors, or mixed epithelial tumors.

Endometrioid borderline tumors composed of atypical or histologically malignant endometrioid type glands or cysts are often set in a dense fibrous stroma with an absence of stroma invasion. They arise either from the surface ovarian epithelium or from endometriosis and have the potential to progress to low-grade endometrioid carcinoma.

Clear-cell borderline tumors are characterized by atypical or histologically malignant glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma with an absence of stromal invasion. The rarity of clear-cell borderline tumors could reflect the fact that the precursors of clear-cell carcinoma most often have the morphology of endometriosis with atypia rather than a clear-cell neoplasm.

Borderline Brenner tumors have atypical or malignant features of the epithelium but lack stromal invasion. Mixed epithelial borderline tumors are composed of an admixture of two or more of the five major cell types: serous, mucinous, endometrioid, clear cell, and transitional cell. Endometriosis, occasionally with atypia, is found in association with more than 50% of mixed epithelial borderline tumors [32].

PROGNOSTIC PARAMETERS

Prognosis of borderline ovarian tumors is generally excellent; however, 11% of these tumors recur and show malignant transformation in 20%–30% of them [9]. To date, there is no agreement on the definition of prognostic factors in terms of recurrence as invasive disease. Five features were previously thought to be related to poor prognosis based on transformation of borderline tumors to invasive disease: (a) cell type, (b) stage, (c) implant type (for serous borderline tumors), (d) the presence of a micropapillary architecture (for serous borderline tumors), and (e) microinvasion. The main limitation of the published studies on this topic is that the patients have not been comprehensively intraoperatively staged or sufficiently sampled during pathological examination to exclude occult stro-

mal invasion (at that time, one section per centimeter of maximum tumor dimension were performed) or the follow-up was not adequately long.

The pathological stage of disease and subclassification of extraovarian disease into invasive and noninvasive implants, together with the presence of postoperative macroscopic residual disease, currently appears to be the major predictor not only for recurrence and but also for survival [9, 45, 46]. In a review published in 2000 by Seidman and Kurman involving 245 studies and 4,129 patients, the survival rate for patients with invasive implants was 66% after a mean follow-up of 7.4 years, compared to 95% for patients with noninvasive implants ($p < .0001$) [34]. The survival rate for patients with invasive implants was similar to that for patients with invasive low-grade (micropapillary) serous carcinoma, with a recurrence rate of 30% (mostly as invasive carcinoma), progression-free survival of about 2 years, and a median survival time of 6–7 years [47].

Some studies have not revealed the presence of invasive implants in contrast to noninvasive implants as a negative prognostic factor [46, 48–49]. The explanation of the differences between the results of studies reporting on the potential prognostic impact of peritoneal implant could be related to the different accuracy of implant subclassification (e.g., the recognition of the desmoplastic noninvasive implants from invasive ones, limited size of biopsy without underlying tissue) and to the discrepancies in surgical attempts to stage the disease and to strive to completely extirpate the tumor. It is of note that the micropapillary architecture is strongly associated with invasive implants (45%) in contrast to typical borderline serous tumors (7%) [50]. These findings indicate that further histological sampling of micropapillary borderline tumors may reveal true invasion in some cases; detailed exploration of pelvis and abdomen followed by complete tumor resection (tumor debulking) is required in micropapillary borderline tumors to detect and eventually remove invasive implants.

It has been shown that stromal microinvasion, if unassociated with extraovarian invasive implants, has no effect on the rate of recurrence or the rate of progression to invasive disease, as confirmed in large meta-analysis [34, 51]. Limited data suggest in contrast that the second type of microinvasion (Table 2, so-called microinvasive carcinoma) is associated with a higher risk of recurrence [52].

The data re-evaluating nonserous histotypes demonstrated their excellent prognosis independent to concurrent presence of intraepithelial carcinoma and/or microinvasion. The clinical behavior of tumors meeting the criteria of mucinous borderline tumors of gastrointestinal type reveals a benign behavior with excellent prognosis (survival rate of >99% for mucinous BOTs with or without microinvasion, and a survival rate of >95% for mucinous BOTs with intraepithelial carcinoma). Müllerian types of mucinous BOTs, including very few with implants and intraepithelial and microinvasive carcinomas, have also demonstrated benign behavior [36, 40, 53–54]. The behavior of endometrioid BOTs, including those with microinvasion, has been benign as well [26]. There is virtually no published data on the prognosis of clear-cell borderline tumors

with microinvasion or intraepithelial carcinomas, both of which are exceedingly rare. Among over 50 reported cases of atypical proliferative transitional cell (Brenner) tumors, there has been one local recurrence and no convincing evidence of malignant behavior [26]. No borderline Brenner tumor has metastasized or caused the death of a patient [32]. The prognosis of mixed epithelial borderline tumors is dictated by the dominant cell type tumors [32].

One promising prognostic factor seems to be the evaluation of DNA content. Borderline tumors with aneuploid DNA content have a worse prognosis for recurrence and survival. In large flow cytometric analysis on 370 BOTs reported by Kaern et al., aneuploidy in BOTs was associated with a 15-year survival rate of only 15%, despite the 85% survival rate in the patients with diploid tumors [55]. The prognostic significance of DNA ploidy has not yet been reproduced in prospective studies [56, 57] and is, therefore, not widely used in clinical practice.

It has also been clearly demonstrated that a higher recurrence rate is related to the radicality of surgical procedure (postoperative residual tumor vs. complete tumor debulking, complete vs. incomplete staging, ovarian cystectomy vs. unilateral/bilateral salpingoophorectomy) and to the type of surgical approach (laparoscopy vs. laparotomy). In line with these findings, the presence of gross residual tumor was shown to be associated with an increased risk of progressive disease in patients with invasive implants, with a progression-free interval of 24 months [46]. This association was not statistically significant in patients with noninvasive implants [48]. It is not clear whether the association reflects biologic aggressiveness of a tumor that is widespread and unresectable, progression of a tumor that could have been removed if a more vigorous attempt to resect it had been made, or both. These findings indicate, however, that every effort should be made to remove the tumor completely [46, 58–60].

Lymph node involvement could not convincingly be confirmed to be an independent risk factor [34], and various investigators concluded from these results that systematic lymphadenectomy can be omitted. Nevertheless, with the exception of lymph node dissection, incomplete staging was associated with a higher recurrence rate (11.8% [53/450] vs. 7.1% [16/225]) in comparison to patients with optimal staging [9], which could be explained by occult residual tumor left in situ. In 24.7% of patients (284/1,150) who underwent restaging, the residual tumor was revealed after the restaging procedure. In accordance with this fact, a prolonged progression-free interval was observed if restaging was performed [9]. Nonetheless, the indications for restaging remain controversial, as no differences were observed in terms of overall survival between those who were upstaged and those who were not [61–63].

Primary ovarian borderline tumors usually affect patients at the reproductive age, when the preservation of childbearing potential plays a very important role. However, conservative treatment (i.e., the preservation of at least the uterus and one ovary) does increase the risk of disease recurrence in the remaining ovary due to the possibility of bilateral synchronous

tumors or occult metastases left in situ. Not only was serous histotype identified as a significant risk factor for recurrence due to its higher frequency of bilateral ovarian involvement, but the mucinous histotype was also related to a higher recurrence rate if treated only with cystectomy when the definition of free tumor margin is limited [64, 65]. There is also a risk of inadequate histological sampling of a small part of an invasive carcinoma within a large mucinous tumor (particularly among the intestinal subtype), contributing to an increased recurrence rate after a cystectomy [66].

After conservative surgery, the median number of relapses in most series is nearly 15%, compared to 5% in cases of radical surgery [9, 67]. This recurrence rate is even higher after cystectomy (between 12% and 58%) than after oophorectomy (0% and 20%) [14, 68]. However, no data showed the influence on survival because recurrence in the form of an invasive tumor in the remaining ovary is very low—less than 1% for early stages [14, 69–71]. Despite this, to avoid recurrence and still maintain fertility, it seems reasonable to prefer unilateral oophorectomy instead of cystectomy when the contralateral ovary is present and normal.

Concerning the indication of conservative treatment in higher stages of the disease, there is data on conservative management in serous BOT with peritoneal implants showing that the strongest prognostic factor in patients with an advanced-stage borderline tumor is again the use of conservative surgery, with a relative risk for recurrence of 5.4 (95% CI: 2.9–10.1) [49]. The recurrence rate in advanced BOTs treated conservatively is more than three times higher than after radical surgery (44.8% [94/210] vs. 13.7% [50/366]) [9]. When this information on the higher recurrence rate of conservatively treated advanced BOTs is combined with evidence that invasive implants are the most important negative prognostic factor for recurrence in the form of invasive disease [72], many centers propose conservative surgery only to a selected group of patients with noninvasive implants as well as recommending complete resection of peritoneal spread [14, 72–73].

Several retrospective studies reported on the outcome of BOTs after laparoscopy and compared these findings with the outcome after laparotomy. In a review conducted by du Bois et al., it was noted that the recurrence rate was twice as high after conservative laparoscopic surgery than after a laparotomic approach [9]. It seems that the higher risk of relapse is probably not associated with the reduction in overall survival [74]. At any rate, the cumulation of risk factors significantly associated with laparoscopy, such as cyst rupture or incomplete staging [75], should be avoidable if this procedure is performed by an experienced oncologic surgeon.

Adjuvant treatment (chemotherapy, radiotherapy) tends to worsen the prognosis of BOT patients [46, 76], increase toxicity (small bowel complications after radiotherapy, neurotoxicity or bone marrow toxicity), and increase mortality due to treatment complications rather than the disease itself [71, 72]. Therefore, current guidelines do not recommend adjuvant treatment, even for patients with advanced BOTs.

DIAGNOSIS

Almost 30% of patients with BOTs are asymptomatic; approximately 50%–60% of patients complain about nonspecific symptoms (abdominal pain or abdominal distension) and 10% complain of bleeding abnormalities [9, 15]. Most BOTs are detected by ultrasound. Ultrasound is broadly accepted as a highly accurate preoperative method in discriminating between benign and malignant adnexal masses if performed by experienced ultrasound examiner [77–79]. However, correctly classifying BOTs in terms of specific diagnosis based on subjective evaluation of grayscale and Doppler images and the confidence with which the diagnosis is made is difficult [80–82]. The various histological types of BOTs have different gross appearances (Table 3) together with different sonographic features; however, these may overlap with the gross appearances and sonographic features of benign and invasive ovarian tumors.

Serous and endocervical-like mucinous borderline ovarian tumors (Figs. 1, 2) had very similar sonographic features, a smaller diameter, fewer locules, higher numbers of papillary excrescences, and higher color scores inside solid components than mucinous BOTs of intestinal types [83]. They often manifest as unilocular-solid or multilocular-solid tumors with irregular and perfused papillary projections without other signs of complexity, such as a solid pattern, irregular septae, and irregular inner walls due to tumor deposits in young women [81–86]. Their cyst fluid can be anechoic or have low-level or ground-glass echogenicity.

Mucinous intestinal-type BOTs have different sonographic features from other common borderline tumors. They are typically unilateral (>95%), large (20–22 cm), multilocular tumors with >10 locules, a smooth inner lining, echogenic cyst fluid (low level or ground glass), and a smooth outer surface (Fig. 3) [83]. The presence of bilateral mucinous tumors suggests the possibility of metastatic tumor from another side (primarily the gastrointestinal tract). In slightly more than half of mucinous intestinal-type borderline tumors, a “honeycomb nodule,” defined as a multilocular nodule arising from the inner cyst wall (Fig. 3), is present [84].

Some BOTs are barely distinguishable from benign or invasive ovarian tumors. In particular, mucinous intestinal-type BOTs are often misclassified as benign mucinous cystadenoma in 16% (9/55) of patients, as reported in the study by Sokalska et al. [87]. There are also cases of purely unilocular smooth cysts being histologically serous or mucinous BOTs; the incidence of such findings ranged between 3.5% and 11.4% depending on the size of the tumor [83–85]. Papillary projections are more common in borderline tumors than in invasive cancer, but they may also be seen in benign tumors (e.g., serous cystadenomas, serous cystadenofibromas, endometriomas) and lead to many false-positive ultrasound diagnoses of malignancy, particularly to diagnoses of BOTs [85–89]. In comparison with their benign counterparts (serous cystadenomas), serous borderline tumors have usually more numerous, larger (1–10 mm in greatest dimension), and softer papillations. They may secrete a fluid that has higher mucin content than serous cystadenomas, and they are bilateral in

Table 3. Gross appearances of primary ovarian borderline tumors [26]		
Histotype	Subtype	Characteristic macroscopic features
Serous	Typical	Typical serous BOTs can be bilateral in ~30% of patients and are associated with extraovarian lesions involving the peritoneum (so-called implants) in 35% [32].
	Micropapillary	Bilaterality (75%), exophytic growth (54%), and peritoneal implants (50%) are more common with micropapillary subtype; mean size is ~8 cm.
Mucinous	Intestinal (gastrointestinal)	Unilateral, large multilocular or multilocular-solid lesion with mean size of 20–22 cm.
	Endocervical-like (seromucinous, Müllerian)	Smaller, much less common, more frequently bilateral (20%–30%), unilocular-solid or multilocular-solid lesions with eventual implants. Endocervical-like mucinous borderline tumors mimic serous borderline tumors.
Endometrioid		Size average of 8–10 cm, cystic-solid tumor, predominantly unilateral (bilateral only in 4%). Extraovarian disease may be found. Hemorrhagic, green, or brown intracystic fluid.
Clear cell		Clear cell tumors resemble endometrioid tumors on gross examination and cannot be distinguished with any reliability from serous tumors. Size averages 15 cm, with a smooth lobulated external surface. Cut surfaces have a fine honeycomb appearance with minute cysts; the cyst fluid is clear. Peritoneal implants have not been described.
Brenner (transitional cell)		Large solid-cystic tumor with polypoid projections into the cyst lumens. They are always unilateral, larger tumors with mean diameter of 18 cm, confined to the ovary.
Abbreviation: BOT, borderline ovarian tumor.		

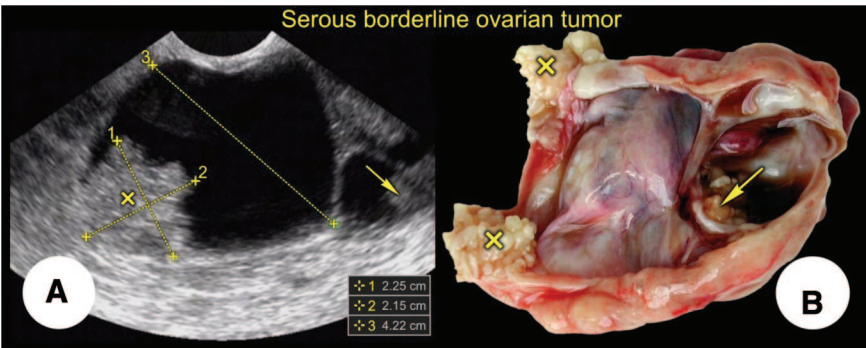


Figure 1. Serous borderline tumor (transvaginal scan). Multilocular-solid tumor with papillae, rather smooth inner cyst wall, and regular septa and anechoic intracystic fluid.

one-third of cases (only one in six serous adenomas are bilateral).

Similarly, there are no reliable sonographic variables to differentiate BOTs from invasive tumors, except the presence of ascites ($p = .0082$) as reported by Valentin et al. [81] and eventually additional clinical information considering the younger age of BOT diagnosis. The mean age for BOT diagnosis is 10 years younger than that of epithelial ovarian cancer [14]. Early-stage low-grade serous carcinomas manifest bilaterally with the same frequency as micropapillary serous borderline tumors (two-thirds are bilateral as compared to only one-third of typical serous borderline tumors)

[90]. Because of the lack of prominent sonographic features, BOTs are also often misdiagnosed as primary invasive tumors [85], particularly as early-stage low-grade ovarian cancer [81]. In the study by Sokalska et al., 24% (13/55 cases) of borderline tumors were presumed to be invasive ovarian tumors [87]. For instance, unilocular or multilocular solid tumors with irregular papillary projections, irregular inner wall linings, and extracapsular growth (as observed not rarely in the micropapillary type of serous BOTs or endocervical type of mucinous BOTs) are not differentiable from invasive tumors on ultrasound (Figs. 1, 2). This finding is in line with a theory of evolution of a subset

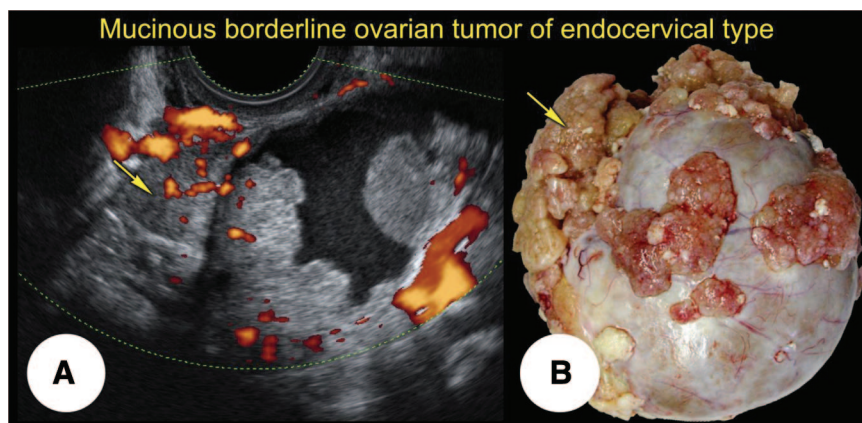


Figure 2. Mucinous borderline tumor of endocervical type (transvaginal scan). Multilocular-solid tumor with larger number of endophytic and exophytic tumor papillae, high intrapapillary flow density, and intracystic fluid with low-level echogenicity.

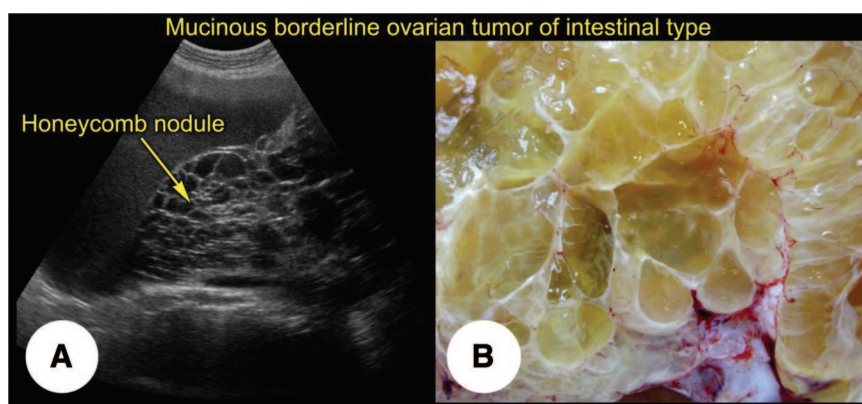


Figure 3. Mucinous borderline tumor of intestinal type (transabdominal scan). Large, multilocular tumor with “honeycomb” nodule on the posterior inner wall and intracystic fluid of low-level echogenicity.

of ovarian cystadenomas through borderline tumors to low-grade epithelial ovarian cancer [90].

For all these reasons, BOTs are correctly preoperatively classified only in 29%–69% of cases [84, 87, 91–92]. Doppler examination of tumor vascular patterns (color content of the entire tumor and of the solid parts of the tumor, approximate estimation of the blood flow velocities) increased the percentage of correct specific diagnoses in only 5% of cases [91]. The lack of muscular elements results in a low resistance to blood flow and arteriovenous anastomoses give high pressure gradients, resulting in high-velocity blood flow. But the studies revealed no specific Doppler flow indices currently available to diagnose BOTs [85, 86]. The absence of perfusion in the solid portion of tumor, with no detectable vessels in color Doppler, may represent a marker of benign tumor. A subjective semi-quantitative assessment of the amount of intrapapillary blood flow revealed fewer signals in benign tumors (3%–4%) than in malignant tumors (30%) [89]. The rate of intrapapillary flow was similar between borderline (56.3%) and invasive tumors (66.7%) in another study [85].

The more detailed and noninvasive evaluation of angiogenesis can be made by the use of intravascular contrast agents, which improve the detection of low-volume blood flow

by increasing the signal-to-noise ratio. Even though the findings of contrast-enhanced ultrasound examination differed between benign and malignant tumors in the studies addressing this topic, there was a substantial overlap in contrast findings between benign and borderline tumors [93, 94].

Another new ultrasound technology, the three-dimensional (3D) ultrasound, adds also very little in specific diagnosis of BOTs [95]. The 3D grayscale ultrasound was not superior to conventional two-dimensional (2D) ultrasound, although the 3D image can help to evaluate the internal cyst wall of the mass and to look for irregularities or solid papillary projections. The assessment of vascularization using 3D power Doppler (3D-PD) ultrasound also allows objective analysis of the quantitative power Doppler variables using specialized software and of the vessel morphology (the tumor vascular tree) in the solid portion of tumor. The vascular tree used to be different in malignant and benign tumors showing microaneurysms, arteriovenous shunts, abnormal vessel branching, tortuosity and vessel caliber changes characteristic of malignant tumors. The objective quantification of tumor vascularity allows detection of the microvessel density assessed as 3D-PD vascular indexes, which are significantly higher in tumoral tissues than in benign tissue. However, the studies addressing either vascular

tree assessment for predicting ovarian malignancy or the use of 3D-PD vascular indexes in ovarian masses revealed no statistical differences or controversial results when compared to 2D ultrasound [95].

There are known limitations to making specific diagnoses of BOTs, even in the hands of an ultrasound expert. However, ultrasound can provide not only a detailed view of the pelvis (usually by transvaginal scan), but it can also detect the peritoneal implants on transvaginal and transabdominal scans with high accuracy (91%–95%; Fig. 4) [96] and provide information for preoperative planning and staging [97].

Because the other modern imaging techniques are also based on the assessment of tumor morphological and vessel patterns, their results are also limited by the overlap of macroscopic features between benign and malignant ovarian tumors. For that reason, there is no additional benefit to using conventional computed tomography, magnetic resonance imaging, or even positron emission tomography in the diagnosis of BOTs. These approaches lead to extra costs and patient discomfort. There is data reporting the usefulness of magnetic resonance imaging in recognizing specific types of tissue (e.g., blood, fat, fibrous tissue) based on signal properties; it allows confident diagnosis of benign ovarian lesions such as hemorrhagic cysts, endometriomas, dermoid cysts, and fibromas or thecomas, as well as data regarding the benefit of computed tomography in the identification of fat components in dermoid cysts [98]. However, these masses are not the diagnostic problem with routine ultrasonography [99]. Neither computed tomography nor magnetic resonance imaging can reliably discriminate between BOTs and early-stage low-grade ovarian cancer or benign masses with papillary projections [100]. Positron emission tomography/computed tomography actually has a risk of false-negative interpretation of borderline tumors due to the cystic portion of the tumor [101, 102].

In 2011, it was recommended by the National Institute for Health and Clinical Excellence to first test for biomarker CA125 in patients with symptoms suggesting the presence of a malignant ovarian tumor, with only those patients with elevated CA125 levels (≥ 35 U/mL) being referred for an ultrasound scan [103]. There is a lot of criticism concerning this clinical guidance, including the risk of underdiagnosing the majority of BOTs if this protocol is followed because the serum tumor marker CA125 is often negative in patients with borderline tumors [104]. In the systematic review by du Bois et al., CA125 levels were negative ($CA125 \leq 35$ U/mL) in 53.8% of the 1,937 patients with borderline tumors [9]. In the multicenter prospective International Ovarian Tumor Analysis (IOTA), an ultrasound study of ovarian masses, BOTs were found in 93 (5%) of 1,918 patients with no previous history of malignancy; CA125 levels were negative in 53% of these patients. Specifically, the CA125 median value reached 35 U/mL (interquartile range: 19–105 U/mL) for patients with newly-diagnosed BOTs [92].

Indeed, there is a high risk of false-positive CA125 results due to a variety of clinical variables, such as menstruation, ovulation, endometriosis, liver disease, inflammatory disease, and functional cysts, which may potentially lead to a large

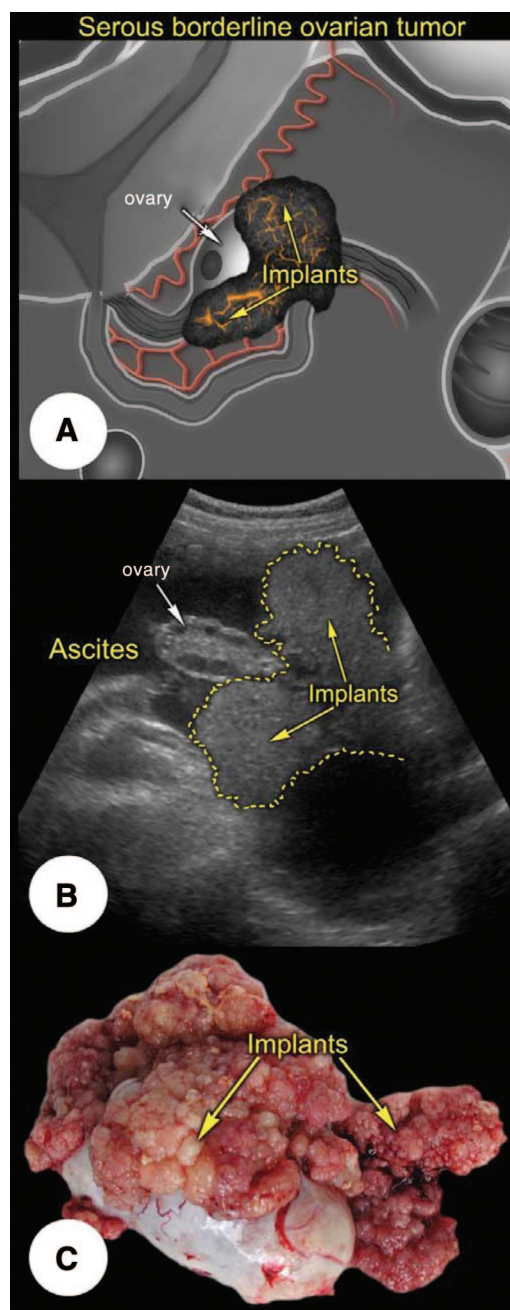


Figure 4. Exophytic implants on the surface of contralateral ovary (transabdominal scan). Hyperechogenic implants surround the contralateral ovary without involvement of ovarian stroma.

number of unnecessary ultrasound examinations and interventions. A combination of CA125, human epididymis secretory protein 4, and menopausal status to predict the presence of a malignant ovarian tumor (the risk of ovarian malignancy algorithm, so-called ROMA algorithm) also did not perform better than ultrasound assessment of adnexal masses (area under the curve: 0.893 vs. 0.968) [104].

In line with the low performance of CA125, the risk of malignancy index (RMI), developed by Jacobs et al. in 1990 [105], did not perform well for patients with BOTs. The RMI is

a scoring system derived from a logistic regression formula that combines menopausal status with the serum CA125 level and ultrasound variables. However, the performance of RMI is poor when applied to masses in young women and pathology that is difficult to be characterised with ultrasound; also, the sensitivity of the test is low. In a study by van Holsbeke et al., the RMI missed 73% of BOTs (31/42 cases) [106].

In summary, according to the presented data, borderline tumors belong to a group of masses that are difficult to correctly classify using subjective assessment (i.e., subjective evaluation of grayscale and Doppler ultrasound findings by an experienced ultrasound examiner, also called pattern recognition). For such masses, it is therefore necessary to use methods other than subjective assessment. It is due to these factors that the measurements of the serum CA125, calculation of the RMI, use of logistic regression models based on ultrasound variables [107], and use of ultrasound simple rules [108] were evaluated. However, their results were inferior to subjective assessment of BOTs.

MANAGEMENT OF BORDERLINE TUMORS

The majority of patients with BOTs are frequently diagnosed during their reproductive age. For these patients, therapeutic decisions regarding fertility-sparing surgery, treatment of infertility or premature hormonal deprivation, intra- and postoperative morbidity, and adjuvant chemotherapeutic treatments are particularly pertinent [109]. Currently, no prospective randomized trials are available for clinical management. Therefore, recommendations for counseling and treating patients are mainly based on retrospective analysis and single-center experiences.

Conservative Surgery

Data from the recent literature are reassuring regarding the efficacy and safety of conservative surgery (i.e., involving the preservation of the uterus and at least part of one ovary, with comprehensive surgical staging) for borderline tumors of the ovary in all stages [68, 70, 110]. When conservative management is not feasible because of massive bilateral ovarian tumor involvement, at least the uterus can be preserved for eventual transfer of frozen embryos obtained before radical surgery. The available data suggest that the rate of recurrence is higher after conservative surgery (10% to 20% vs. approximately 5% for radical surgery) [111]. The recurrences are nevertheless almost always from borderline tumors (not invasive disease) [92] and are found on the spared ovary. For patients with early-stage disease, the extraovarian recurrence only occurs in 2% of patients compared with 20% of patients with advanced disease (FIGO stages II-III) [9]. Concerning the indication of conservative treatment in higher stages of disease, conservative management should be limited to a select group of patients with complete resection of peritoneal spread and noninvasive implants.

Cystectomy is associated with a higher recurrence rate (up to 31%) [9]. For that reason, cystectomy should be performed only for patients with bilateral tumors and/or only one ovary. The exception to this rule is very young patients for whom the preservation of the maximum amount of ovarian tissue is at-

tempted and the possible recurrence can be detected in a timely manner by close follow-up performed optimally by transvaginal scan. The ability of ultrasound to detect very small recurrences encased in normal ovarian parenchyma makes it potentially possible to perform further fertility-sparing surgery, with preservation of an adequate amount of functioning ovarian parenchyma [112]. However, extensive sampling of the resection margins of the removed ovarian cyst is very important [113]. The predictors of relapse after cystectomy are resection margins containing tumor cells or multifocal intraovarian tumor [12] or even intraoperative cyst rupture [114]. The use of cystectomy is not safe in patients undergoing conservative management for mucinous borderline tumors because of an increased risk of recurrence in the form of invasive carcinoma (although this situation is exceptional for serous BOTs) [66].

A random wedge biopsy of the contralateral ovary to exclude an occult concurrent lesion is also not advised because of the risk of postoperative periovarian adhesions leading to the mechanical factor of sterility and low diagnostic rate related to a blind section of macroscopic normal ovary [12]. Based on the fact that serous BOTs often occur bilaterally, the most preferable noninvasive technique to exclude a concurrent contralateral intraovarian lesion is a preoperative transvaginal scan, which provides detail ovarian sonomorphology and vascular patterns. This technique can be also used intraoperatively in cases of bilateral ovarian involvement, allowing the surgeon to achieve macroscopic free tumor margins. Recently, biopsies of the contralateral ovary have been performed only in cases of suspicious macroscopic lesions.

If a relapse in the remaining ovary occurs, further conservative management may be offered to patients who plan further pregnancies. Such treatment should be reserved for patients without invasive implants who are young (age <40 years), desire fertility preservation, and engage in long-term follow-up. However, if at the time of clinical relapse an invasive disease is found, complete debulking is recommended without sparing fertility. Removal of the preserved ovary after patients complete their fertility plans depends on several factors such as histologic subtype, FIGO stage of disease, type of conservative surgery, and the patient's own wishes. Based on the fact that most recurrent diseases are of the borderline type, easily curable, and with excellent prognosis, several teams suggest that systematic removal of the remaining ovary after childbearing is not mandatory as long as the patients engage in regular, close follow-up examinations [15]. Nevertheless, the psychological impact of waiting for relapse is considerable and there is still a risk for development of invasive ovarian tumors. Therefore, other authors recommend definitive surgery after family planning is completed [11, 111]. To achieve low morbidity related just to the completion of salpingo-oophorectomy, a concurrent hysterectomy can be avoided because no solitary recurrences in the uterus have been observed [71].

Intraoperative Diagnosis and Staging

To establish a complete FIGO staging, a combination of intraoperative exploration of the entire abdominal cavity should be

conducted, with peritoneal washings, omentectomy, multiple peritoneal biopsies, and complete resection of all macroscopic suspected lesions. For resection of the primary tumor, bilateral salpingo-oophorectomy in combination with hysterectomy is recommended. Lymphadenectomy is not indicated because the recurrence and survival rates for patients with positive or negative lymph nodes were similar [9, 34].

Optimal staging allows a correct pathological diagnosis to be obtained based on the entire tumor tissue and to define a group with a higher risk of recurrency. The staging surgery could be performed at the time of surgical treatment of the ovarian tumor when fresh frozen section analysis has confirmed the diagnosis of borderline tumor or during a restaging surgery when the borderline tumor was diagnosed by permanent histological analysis after the first surgery. In approximately a third of cases, the diagnosis must be revised using permanent sections; there is a greater tendency to underdiagnose borderline tumors as benign tumors on frozen section examination (24.1%–30.6%) than to overdiagnose them as carcinomas (6.6%–9.9%) [9, 115]. In addition, approximately 20%–30% of ovarian tumors diagnosed as borderline ovarian tumors at the time of frozen section examination prove to be carcinomas on further sampling—more so for mucinous tumors than serous tumors (33% vs. 13%, respectively) [9, 15, 26]. Only occasionally is a BOT diagnosis from a frozen section further reclassified as a benign tumor using permanent sections (5% of cases).

Although there is widespread agreement on the histologic appearances of BOTs, it must be recognized that extensive specimen sampling is required to firmly establish the diagnosis, especially in mucinous tumors. This sampling is not always possible during intraoperative diagnosis, which needs to be recognized by both the pathologist and the operating surgeon to minimize inappropriate initial surgical therapy. Therefore, in all cases of surgically treated ovarian lesions, careful exploration of the abdominal cavity and resection of all macroscopic lesions seems to be advantageous, whether or not the mass is presumed to be of benign origin. This approach avoids surgical restaging in many cases.

There is a great deal of debate regarding the prognostic benefit of complete staging if macroscopic exploration is normal—in particular, whether omentectomy, hysterectomy, and appendectomy should be performed in such a situation. Because only 15% of unilateral tumors are associated with extraovarian disease, complete formal staging is probably not necessary for a unilateral ovarian tumor unless suspicious peritoneal lesions or micropapillary patterns are found. However, careful intraoperative exploration cannot be omitted.

It should also be noted that 56% of bilateral tumors are associated with extraovarian disease. Micropapillary borderline tumors often present bilaterally and with invasive implants; therefore, complete staging in this setting is advisable to perform sampling of as many implants as feasible [26]. The omentum is the most likely site for invasive implants [32, 68]. Therefore, surgeons must take a sufficient amount of omental tissue to enable the pathologist to distinguish noninvasive from invasive implants. In turn, the pathologist must assess multiple

samples of macroscopically “normal”-appearing omentum to ascertain adequate sampling. Earlier studies showed that relapse occurred in 4 of 45 patients in whom omentectomy was not performed, indicating the presence of occult residual tumors that was left in situ [12].

Some authors have questioned the role of hysterectomy in cases where no peritoneal implants on the surface of the uterine serosa are present [9, 14]. Menczer et al. showed a low rate of uterine involvement among patients with BOTs who underwent hysterectomy in addition to bilateral adnexectomy [58]. Uterine involvement was present in only 3 of 147 patients (2%). When intraoperative consultation with frozen section leads to a diagnosis of a mucinous ovarian tumor, especially in the setting of pseudomyxoma peritonei, the need for appendectomy should be conveyed to the surgeon so as to not misdiagnose the primary low-grade appendiceal mucinous neoplasm. Otherwise, the performance of appendectomy seems to be optional at the time of surgery: no histological evidence of appendiceal involvement was found in 57 patients with apparent early-stage ovarian malignancy, including 15 BOTs, in a recent series from the MD Anderson Cancer Center [65].

Surgical Approach (Laparoscopy/Laparotomy)

Laparoscopy is more frequently used for conservatively treated patients. Laparoscopic management of borderline ovarian tumors is associated with a higher rate of cyst rupture and incomplete staging [75]. In a review conducted by du Bois et al., a higher recurrency rate was observed after laparoscopically performed conservative surgery than after a laparotomic approach (14.9 vs. 7.7%) [9]. In another two studies—an Italian and a French multicenter study—the type of surgical approach (laparoscopic vs. laparotomic) did not seem to influence the progression-free interval and rate of relapse [75, 116]. In addition, laparoscopy seems to be an attractive approach supported by lower morbidity and fewer adhesions, which are important for fertility [117]. Determining whether a laparoscopic approach or conservative surgery influence the recurrency rate is difficult because cystectomies and other conservative surgeries are often performed laparoscopically rather than by midline laparotomy, and the outcomes after laparoscopy versus laparotomy are evaluated mainly from retrospective studies. All laparoscopic procedures should nevertheless be performed by oncologic surgeons trained in extensive laparoscopic procedures in order to obtain optimal surgical staging, complete debulking, and better results in terms of both relapse-free survival and fertility preservation rate [116].

POSTOPERATIVE TREATMENT

Adjuvant Treatment (Chemotherapy, Radiotherapy, Hormonotherapy, and Targeted Therapy)

To date, there is no clear evidence that chemotherapy can decrease relapse rates or improve survival in any subset of patients with diagnosed BOTs [15, 68, 72, 76]. BOTs treated with adjuvant chemotherapy or radiotherapy showed high persistent or recurrent disease (up to 40%) [9]. Poor response rates to

traditional cytotoxic agents might be explained by the low proliferation rate of BOTs in general. More than 90% of serous borderline ovarian tumors are estrogen-receptor positive [118], but there are only case reports of major responses to tamoxifen, leuprolide, and anastrozole [119]. The cytostatic effect of medroxyprogesteron acetate has also been evaluated [120]. The effect of antiangiogenic or other newer-targeted agents on these tumors is not known. Because serous borderline tumors have a high frequency of mutations in *KRAS* and *BRAF*, future clinical trials should help to determine if MEK inhibitors or other anticancer agents targeting the pathway RAS/RAF/MEK/MAPK can prolong the disease-free interval and overall survival times in patients with advanced stage disease. The drug-induced inhibition of PI3K/PTEN signaling pathway defects, which are often found in endometrioid or clear-cell borderline tumors, may similarly provide treatment alternative in BOTs.

Treatment of Infertility

Spontaneous conception is reported after conservative surgery in 50% of patients without any deterioration in the survival rate [14]. However, infertility is frequently observed in patients with BOTs. Up to 35% of these patients have a history of infertility before treatment [12]. Surgical treatment of BOTs can also cause postoperative infertility due to adhesions and insufficient residual ovarian tissue after resection. Conservative surgery should be offered with caution to patients aged >40 years. In a large multicenter study published by Fauvet et al., no pregnancies occurred in this age group [121].

Some studies noted an elevated risk of borderline ovarian tumors following the use of fertility drugs; however, short follow-up, low statistical power, and lack of control have limited the conclusions from previous studies. A recently published large nationwide cohort study in the Netherlands with a median follow-up of 15 years shows that women treated with ovarian stimulation for in vitro fertilization (IVF) have a two-fold increased risk of borderline tumors, especially of serous histotype, compared with subfertile women not treated for IVF [8]. In addition, with a prolonged follow-up 15 or more years after the first IVF treatment, they also observed the increased risk of primary ovarian carcinomas; the standardized incidence ratio was 3.54 (95% CI: 1.62–6.72). Therefore, until more data from larger prospective cohort studies of IVF-treated women with prolonged follow-up and a comparison group of subfertile women not treated with IVF are available, all patients with previous history of BOTs should receive detailed counseling regarding the potential risks associated with ovarian stimulation and should undergo close follow-up during and after IVF therapy.

In cases with extensive tumor involvement of both ovaries or the remaining ovary with or without uterine serosa infiltration, fertility-sparing surgery may not be possible. However, the preservation of germ cells and other fertility techniques considering the patient's desire must be taken in account. A conceptual framework for managing concerns about fertility at the time of malignant tumor diagnosis is presented in a review conducted by Jeruss and Woodruff [122]. It is due to these fac-

tors that the treatment of patients with BOTs should be made in a multidisciplinary setting of reproductive medicine, gynecologists, oncologists, and others.

Treatment of Hormone Deprivation

Hormone replacement therapy (HRT) to prevent cardiovascular disease and osteoporosis and improve quality of life is an important issue, as many patients with BOTs are relatively young women. HRT should be offered to these patients [109].

Treatment of Recurrences

In the case of relapse on the remaining ovary in the borderline form after conservative surgery, another conservative surgery (cystectomy) may be proposed for these patients to preserve fertility as described previously. If the preservation of fertility is not desired, bilateral salpingoophorectomy with or without hysterectomy is performed.

When extraovarian recurrence in the form of borderline tumor or invasive disease occurs, extensive cytoreductive surgery, in line with the surgical management of primary ovarian cancer, is the treatment option of choice. Residual tumors at the completion of secondary debulking are an important prognostic factor: 12% of patients with optimal debulking died of disease compared with 60% of patients whose tumors were suboptimally debulked [123]. This is especially pronounced because the recurrences in the form of borderline tumors or well-differentiated carcinomas have a low response rate to platinum-taxane therapy. In a review by du Bois et al., only 15.1% (8/53 patients) and 11.3% (6/53 patients) of patients had complete or partial response to chemotherapy-treated recurrent tumors [9].

FOLLOW-UP

Regular and intensive follow-up of the patients is essential for the early detection of recurrence in the form of borderline or invasive disease. This must be conducted for a longer period of time than for patients with ovarian cancer. Studies have reported cases in which relapse and death occurred after more than 10–15 years [9, 34, 124–125].

In the case of very late recurrences, it may be difficult to distinguish between recurrence of the initial borderline tumor and a new primary tumor. However, this distinction does not seem to change further management and late recurrences are considered as a recurrence from the initial tumor. The overall recurrence rate for patients previously treated for BOTs is estimated to be up to 11% [9]. Malignant transformation describes the situation in which borderline tumors develop recurrent disease in the form of invasive cancer, which is largely dependent on the length of follow-up. If the follow-up is prolonged after the 5-year period, one-third of all recurrences manifest in the form of invasive disease [9]. The absolute rate for malignant transformation of previous BOTs is about 2%–4% [9, 31]. Usually these malignant tumors are low-grade carcinomas, but in rare cases, serous borderline tumors transform into high-grade serous carcinomas.

The importance of close follow-up is stressed in the literature. Studies specifically addressing the optimal follow-up mo-

dalities and more individualized surveillance strategies related to the higher risk group for recurrency are still missing. In line with prognostic significance as described previously, patients with one or more negative prognostic factors (advanced stage disease and invasive implants, residual tumor, micropapillary borderline and/or microinvasive tumors [specifically type II microinvasion], conservative surgery, incomplete staging) should be followed very closely and for adequate period of time in line with FIGO guidelines [126]. Follow-up is usually a combination of clinical examination, ultrasound, and CA125 levels. Because mucinous tumors often do not express CA125 [127], some authors suggest that CA19–9 can be used for the evaluation of these tumors instead [128]. The level of serum tumor marker is usually followed in patients who displayed positive levels of CA125 or CA19–9 in their primary diagnosis of BOTs. During the initial 2 years, follow-up evaluation is performed every 3 months. Patients are then evaluated biannually for 3–5 years after surgery, and then annually thereafter [68].

Transvaginal and transabdominal ultrasound are currently the optimal techniques for the surveillance of patients treated for BOTs because of their high ability to detect discrete intraovarian abnormalities as well as extraovarian implants when performed by an experienced examiner [96, 97]. Specifically in conservatively treated patients, recurrent tumors predominantly manifest in the ovaries, where the transvaginal scan plays an invaluable role, as was demonstrated by IOTA. In the scope of this large international multicenter ultrasound study on ovarian masses involving 1,938 ovarian tumors and subanalysis of new and recurrent primary ovarian borderline tumors in the ovaries, it was shown that BOT history was a strong predictor of BOT in a recurrent ovarian mass (85%). Borderline history awareness significantly improved the sensitivity of ultrasound in making the specific diagnosis of borderline tumors. For patients with a history of BOT, a subjective assessment to diagnose a borderline tumor had a sensitivity of 94% (16/17) and a false-positive rate of 33% (1/3), whereas for patients with no previous history of any ovarian malignancy, sensitivity was 58% (54/93) and the false-positive rate was 5% (85/1812) [92].

The IOTA study also showed that CA125 and symptoms are of limited value in follow-up. CA125 levels were negative in 76% of recurrent BOT, with a median value of 33 U/mL (interquartile range: 13–60 U/mL) for recurrent BOT [92]. According to the symptoms, no patients in IOTA with recurrent ovarian BOTs felt pain during ultrasound examination, which can be easily explained by the fact that the recurrent tumors tend to be significantly smaller (median volume: 41 mL) as opposed to those patients with newly found BOTs with a median tumor size of 548 mL, for which approximately 10% of patients complained of pain [92].

There are also serious limitations of gynecologic examination after conservative treatment. The clinical examination may not allow discrimination of benign masses from malignant ones, especially if the malignant ones manifest as encapsulated lesions with a smooth surface [127].

FUTURE STUDIES

The objective view on BOTs to date is limited by a lack of prospective multicenter large studies with a consensus on histological characteristics among pathologists to reduce interobserver variability, an appropriate protocol for intraoperative staging performed by experienced surgeons, and long-term surveillance of these patients. We are currently awaiting the results from large multicenter analysis of BOTs initiated by the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie). The BOTs included in this analysis were confirmed by reference pathology. Subsequent analyses of patient data should increase knowledge about clinical risk factors, histopathological markers, and the pathogenesis of this disease.

In many centers, the preoperative diagnosis of BOTs is insufficient and the role of ultrasound in this setting is underused. The IOTA study showed that preoperative subjective assessment of benign and malignant ovarian tumors is possible and reached sensitivity of >90% when performed by an experienced sonographer. However, a specific diagnosis of BOTs remains difficult and reached sensitivity of only approximately 60%. The IOTA study designated different mathematical models to calculate the individual risk of malignancy and developed simple ultrasound rules to differentiate benign and malignant tumors. Unfortunately, subjective assessment as well as the mathematical models or simple rules do not perform very well in BOT diagnosis [107, 108]. Therefore, second stage testing (biomarkers, proteomics, 3D ultrasound) to ascertain the preoperative diagnosis of BOTs is needed. The third phase of the IOTA study (2010–2012) was recently concluded; conventional and novel algorithms (including proteomic patterns), which can be used effectively to classify such difficult adnexal masses, were tested prospectively in centers throughout the world. The results from this study are expected soon.

KEY ISSUES

Borderline ovarian tumors have an excellent overall survival rate (FIGO stage I: 95%, FIGO stages II–IV: 70%–85%), with recurrency rate of 11% and absolute risk of invasive disease development (i.e., malignant transformation) of 2%–4% (i.e., 33.3% of all recurrences).

The molecular changes in BOTs indicate that BOTs progress to low-grade carcinoma via the “low-grade pathway.” This pathway involves mutations in RAS/RAF/MEK/MAPK pathways and allelic dysbalances on chromosome I. On the contrary, molecular features (p53 inactivation, LOH at chromosomes 13 and 17) typical for type II tumors (high-grade carcinomas) can help to identify a subpopulation of BOTs tending to aggressive biological behavior.

Negative prognostic factors for recurrence and malignant transformation are FIGO stage and, for more advanced disease, the presence of invasive implants and/or the presence of postoperative macroscopic residual disease. Whether the micropapillary pattern alone implies an unfavorable prognosis is not confirmed by all investigators, but all studies revealed that micropapillary tumors, if associated with invasive implants, behaved more aggressively. Recurrence in the form of BOTs is noted more often after conservative treatment, but these cases

can be detected with close follow-up and can be treated accordingly with an excellent long-term survival.

The preoperative imaging method of choice is ultrasound. Serous borderline tumors and mucinous endocervical-like borderline tumors are more likely to evidence bilaterality than their benign counterparts, similar to that of early stage low-grade cancer. On the contrary, mucinous intestinal-type BOTs are usually unilateral, whereas bilaterality supports the suspicion of secondary ovarian involvement from the gastrointestinal tract.

BOTs are difficult masses to correctly classify preoperatively because their macroscopic features may overlap with invasive and benign ovarian tumors. A correct preoperative diagnosis is made only for one- to two-thirds of patients. Maximum effort is dedicated to seeking an appropriate second-stage test to ascertain the preoperative diagnosis and prognostic parameters in individual tumor types (e.g., biomarkers, proteomics, high resolution 3D ultrasound, molecular genetic alterations, DNA ploidy). To make a specific diagnosis, it is helpful to know that BOTs tend to occur in women about 10 years younger than what is seen with invasive disease; in addition, the presence of ascites is extremely rare in BOTs (9%), as revealed in IOTA.

Borderline ovarian tumors frequently affect women in their reproductive ages, and a more conservative surgery to preserve subsequent fertility is preferred. A conservative approach should be proposed to a select group of patients who wish to preserve fertility, with early-stage mucinous BOTs or completely resected serous BOTs with noninvasive implants, compliance to long-term follow-up, and awareness that there is a higher incidence of relapse compared with radical treatment. The optimal treatment in all types of BOTs is unilateral oophorectomy, which is associated with a lower recurrence rate than cystectomy. Cystectomy should usually be performed in cases of bilateral tumor and/or in patients with only one ovary.

Intraoperative frozen section analysis has a tendency to underdiagnose this disease in 31% of patients as a benign tumor. In such cases, the restaging procedure could be omitted in the absence of micropapillary pattern and if careful intraoperative exploration of the pelvis and abdomen and resection of all macroscopic lesions were performed initially.

Laparoscopy could be employed in the management of

BOTs, but only in the hands of experienced oncologic surgeons to reduce the risk of intraoperative tumor rupture, inadequate staging, and residual tumor disease left in situ, associated with higher recurrency rate. In cases of advanced or recurrent disease, adequate surgery with optimal primary or secondary debulking is needed. To date, there is no proven benefit from adjuvant therapy, even in advanced-stage disease and with the presence of invasive implants.

Follow-up should be based on ultrasound examination, which has proven to be the most effective current imaging method able to explore the pelvis as well as abdomen without any additional risk to patients. Prolonged follow-up (>10 years) is required because of cases of late recurrence. Special attention should be paid to the remaining ovary in conservatively treated patients.

CONCLUSION

Borderline ovarian tumors represent a wide spectrum of tumors with different biological potential and uncertain malignant potential. No precise prognostic or predictive markers exist to clearly distinguish between tumors of purely benign behavior and those with risk of malignant transformation into carcinomas. Therefore, the oncologic safety must be always balanced against less radical treatment.

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